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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/713,928	09/13/96	RADIN	D 7956-011

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EXAMINER	
KEMMERER, E	
ART UNIT	**PAPER NUMBER**
1646	11

DATE MAILED: 02/17/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/713,928	Applicant(s) Radin et al.
	Examiner Elizabeth C. Kemmerer	Group Art Unit 1646

☒ Responsive to communication(s) filed on *Nov 18, 1997*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-50* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *7*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Restriction/Election

Applicant's election with traverse of Group II (claims 39-46) in Paper No. 10 (18 November 1997) is acknowledged. The traversal is partly on the ground(s) that the claimed lysosomal proteins produced in plants have different glycosylation patterns from those found in animal cells or made synthetically. Applicant concludes that the claimed lysosomal proteins cannot be made by a materially different process. This is found to be persuasive, and thus the restriction requirement is *withdrawn*.

Status of Application, Amendments, And/Or Claims

The amendment filed 18 November 1997 (Paper No. 10) has been entered in full. Claims 1-50 are pending and under examination.

The computer readable form and paper copies of the sequence listing have been found to be free of errors and entered into the file.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1646.

35 U.S.C. § 112, First Paragraph

Claims 22-24 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel nucleic acid molecules (i.e., plasmids CTPro1:hGC:FLAG, pCT22, and pCT54) and novel plant lines (X-11, X-27, and CT40-9). Since the nucleic acid molecules and plant lines are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the nucleic acid molecules and plant lines are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules and the plant lines (or seeds thereof). The specification does not disclose a repeatable process to obtain the nucleic acid molecules or plant lines and it is not apparent if the nucleic acid molecules or plant lines are readily available to the public. It is noted that Applicant has deposited some of the nucleic acid molecules and seeds of the plant lines (p. 58 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules and seeds have been deposited under the Budapest Treaty and that the nucleic acid molecules and seeds will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy

the deposit requirement made herein for claims 22-24. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Regarding the deposit of the seeds (claims 36-38), a minimum deposit of 2500 seeds is considered sufficient in the ordinary case to assure availability through the period for which a deposit must be maintained. This also needs to be established on the record as indicated above. Finally, Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." At p. 58, the

ATCC number and date of deposit for plasmid pCT54 are missing. The specification should be amended to include such; however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information.

Claims 1-21, 25-35, and 39-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention wherein the recited *modified* lysosomal enzyme is (1) modified only by the addition of amino acid residues at the N- or C-terminus, and wherein the modified lysosomal enzyme retains the enzymatic activity of the wild-type lysosomal enzyme, or (2) a fragment of the naturally occurring lysosomal enzyme wherein the fragment retains the enzymatic activity of the wild-type lysosomal enzyme, or (3) a conservatively substituted variant of the naturally occurring lysosomal enzyme wherein the variant retains the enzymatic activity of the wild-type lysosomal enzyme, does not reasonably provide enablement for the claimed invention wherein the modified lysosomal enzyme comprises any type of modification, such as internal additions/deletions, non-conservative substitutions, or other chemical modifications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims encompass products and methods relating to the recombinant expression of a lysosomal enzyme, or a modified form thereof, in plant tissue. Whereas most of the claims do not recite limitations regarding the types of modifications that are embraced, claim 10 recites such limitations wherein one or more amino acid substitutions, additions and/or deletions are embraced.

Claims 5, 6, 14, 15, 29, 30, 42, and 43 recite that the modifications can include the addition of a marker peptide. The specification discloses the expression of (1) enzymatically active, modified human glucocerebrosidase (hGC) wherein the modification consists of the addition of a marker peptide (FLAG) to the C-terminus of the hGC, and (2) enzymatically active, modified human α-L-iduronidase (IDUA) in transgenic tobacco plants. The specification also provides enabling guidance regarding how to express wild type human hGC in transgenic tobacco plants. The scope of exclusive right as defined by the claims fails to bear a reasonable correlation with the disclosure for the following reasons. The state of the established that modification of an amino acid sequence by internal additions/deletions of non-conservative substitutions was more likely than not to result in non-functional proteins, and was unpredictable (Bowie et al., Ngo et al., Wells, and Schulz et al.). While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol.247, pp.1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein

which are tolerant to change (e.g. such as by non-conservative amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Due to the large quantity of experimentation necessary to determine which amino acid modifications (other then N- or C-terminal additions/deletions or conservative substitutions) result in retained enzymatic activity after expression in a plant, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art establishing the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite limitations regarding the types of modifications, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 U.S.C. § 112, Second Paragraph

Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 is rendered vague and indefinite due to the recitation of "_____" instead of an ATCC number. Since the ATCC number is not recited in the specification, this is also an issue under 35 U.S.C. §112, first paragraph. See section on 35 U.S.C. § 112, first paragraph, above.

Claim Objections

Claims 8, 20, 21, 39, 45, and 46 are objected to because of the following informalities: In claims 8 and 45, the phrase "any of claims A, B and C" should read "any of claims A, B *or* C." In claims 20 and 21, the recitation of a plant cell, tissue or organ which "has" a recombinant expression construct is confusing. It is suggested that Applicant consider amending the claim to recite that the plant cell, tissue, or construct is transformed with, transfected with, or expresses the recombinant construct. In claim 39, it appears that "transgenic plant **cell** or a cell, tissue or organ" in the second line of part (b) should read "transgenic plant or a cell, tissue or organ." In claim 46, it appears that "glucocerebrosidase **or** modified glucocerebrosidase, α-L-iduronidase or modified α-L-iduronidase" should read "glucocerebrosidase**,** modified glucocerebrosidase, α-L-iduronidase or modified α-L-iduronidase." Appropriate correction is required.

Sequence Rules

The instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825, because the application fails to refer to each disclosed sequence by use of the assigned identifier (i.e., SEQ ID NO:) (37 CFR 1.821(d)). This occurs at least at p. 13, line 33; p. 23, lines 28 and 29; and Figures 1, 11, 19, and 20. Applicant is advised that when a sequence is disclosed in a drawing, the sequence identifier can be referred to in the drawing itself or in the brief description thereof. Applicant's attention is also directed to a possible clerical error in the sequence appearing in Figure 11, where an "S" appears at position 461.

Conclusion

No claims are allowed.

The claims are deemed to be free of the prior art for the following reasons. The claims require the expression of enzymatically active lysosomal enzymes in transformed plant material. Although active enzymes of non-plant origin have been expressed in transformed plant material (e.g., expression of active bovine lysozyme in transgenic tobacco, Mirkov et al., U.S. Patent 5,422,108 of record), there are no examples of the expression of active *lysosomal* enzymes in transformed plant material. Plants do not have lysosomes, although they have somewhat similar structures called vacuoles. The trafficking of endogenous proteins to lysosomes in animals and to vacuoles in plants occurs via different mechanisms (see discussion of this in Cramer et al., ref. AK of record). Therefore, the disclosure in the prior art of the expression of active, mammalian enzymes in transformed plants (e.g., Mirkov et al.) did not render obvious the expression of active *lysosomal* enzymes in transformed plants, because there was no reasonable expectation of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D., whose telephone number is (703) 308-2673. The examiner can normally be reached on Mondays through Thursdays from 6:30 a.m. to 4:00 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Stephen Walsh, Ph.D., can be reached on (703) 308-2957.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**stephen.walsh@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH C. KEMMERER
PATENT EXAMINER

ECK
February 12, 1998